

Melioidosis: an important emerging infectious disease — a military problem?

Air Vice-Marshal Bruce H Short,
RFD, FRACP, FCCP, FACP, FACTM



1. Rice paddy — prime conditions for *Burkholderia pseudomallei*, the causative organism in melioidosis.

MELIOIDOSIS is a collective term for infection caused by the soil organism *Burkholderia pseudomallei*. The causative organism was first described by Whitmore in 1912 when he first isolated *B. pseudomallei* from an opiate addict in Rangoon.¹ Whitmore's name was for some time eponymously linked with the disease melioidosis.

For many years the causative organism of melioidosis was classified within the *Pseudomonas* genus; however, in 1992, along with *P. mallei* and four other species, *P. pseudomallei* was reclassified to a new genus named after the US microbiologist Walter Burkholder. The genus *Burkholderia* comprises at least 12 species, many of which are natural inhabitants of the rhizosphere, the bacteriological and chemical milieu of plant roots.

The first case of human melioidosis in Australia was described in a young diabetic adult from Townsville in 1950 who died of septicaemic melioidosis.² The first case in the Northern Territory was reported a decade later.³ Less than 40 years later, through a combination of increasing incidence and improved diagnostic techniques, melioidosis has become the commonest cause of fatal community-acquired bacteraemic pneumonia at the Royal Darwin Hospital.⁴

Military medical significance of *B. pseudomallei* and *B. mallei*

Melioidosis is one of several emerging infectious diseases that pose a significant community health risk to the people of the "Top End" of the Northern Territory and (to a lesser extent) those of the northwest of Western Australia. In the absence of a suitable vaccine, troop deployments within these areas, particularly during the monsoon, may lead to infections with this potentially lethal microorganism. Both acute illness and reactivated infection, potentially many years later, are associated with high morbidity and mortality. Both *B.*

Synopsis

- ◆ Melioidosis is an uncommon yet potentially fatal tropical and emerging infectious disease which is transmitted by skin puncture with contaminated water and soil.
- ◆ The healthy host uncommonly develops acute disease, but those with diabetes, renal impairment, chronic pulmonary disease, excess alcohol consumption and immunosuppression commonly develop acute disease, often of the severe septicaemic form.
- ◆ Recrudescence melioidosis, sometimes after a very long latent interval, may present as either an acute or subacute syndrome.
- ◆ Early appropriate intravenous antibiotic therapy, followed by at least three months of maintenance antibiotic therapy, is curative.
- ◆ Military deployments, particularly to the hyperendemic regions of the "Top End" of the Northern Territory in Australia or the north-eastern provinces of Thailand during the monsoon, are likely to expose personnel on patrol through paddy fields or contaminated waters to the risks of contracting *B. pseudomallei* infection.

ADF Health 2002; 3: 13-21

pseudomallei and *B. mallei* have been considered as potential agents for biological warfare and biological terrorism.

In humans and animals, primarily horses, *B. mallei* may localise as a subcutaneous form, termed farcy, or disseminate to cause the disease known as glanders. Like melioidosis, glanders is a lethal and contagious disease. During the First World War, Germany engaged in biological sabotage against several countries by releasing cultures of both *B. mallei* and *Bacillus anthracis* to infect livestock that was to be shipped to Allied countries. The objective was to destroy livestock and provide a source of a lethal agent to be transmitted from animals to humans.⁵ In July 2001, the first reported case of human glanders since 1949 occurred in an insulin-dependent diabetic microbiologist working at the US Army Medical

Air Vice-Marshal Bruce Short is the Surgeon General ADF. He is in private practice as a specialist general physician in Sydney.

Bruce H Short, RFD, MB BS, FRACP, FCCP, FACP, FACTM, Surgeon General ADF.
Correspondence: C/- CP2-7-121, Campbell Park Offices, Canberra, ACT 2600.

Research Institute for Infectious Diseases, contracted presumably via transcutaneous puncture with infected material.⁶

Although melioidosis is clinically and pathologically similar to glanders disease, the ecology and epidemiology of the two are entirely different. Unlike glanders, animals do not appear to represent a reservoir for the transmission of human melioidosis.

Epidemiology of melioidosis

Melioidosis is primarily a disease of the tropics (the region between the Tropic of Cancer, 23.5°N, and the Tropic of Capricorn, 23.5°S). Within the tropics, there are two areas where melioidosis may be the most important bacterial human pathogen: the Top End region of the Northern Territory in Australia and some northeastern provinces of Thailand. These two regions may be considered “hyperendemic” for melioidosis.⁷

Almost all cases of melioidosis diagnosed in temperate climates have been imported from the tropics, with the exception of a unique outbreak in France in the mid-1970s.⁸ This occurred in animals in the Paris zoo and spread to other zoos and equestrian clubs in France.⁹ In 2000, the first Finnish case (presenting as a urinary tract infection) was reported in a previously healthy male tourist.¹⁰

In the past decade reports of disease in both humans and animals have increased from countries outside the tropics. A Taiwanese report documents the steady rise of melioidosis in that country, with 17 infections diagnosed between 1982 and 2000.¹¹ Other countries reporting melioidosis include China, especially Hong Kong, Brunei, India, Sri Lanka, Bangladesh, Pakistan and the Philippines. Sporadic cases have also been reported from the Caribbean, Central and South America, Africa and the Middle East. The increasing worldwide reporting of melioidosis underscores an emerging global problem. The highest number of infections are reported from Thailand (with an estimated 2000–3000 cases each year),¹² Malaysia, Singapore and northern Australia. Similar to the experience in Australia, in northeastern Thailand 20% of community-acquired septicaemia is caused by melioidosis.¹³

The average annual incidence of melioidosis in the Top End of the Northern Territory between 1989 and 1998 was 16.5 per 100 000, with a rate of 34.5 per 100 000 for the year spanning the heavy and prolonged 1997–1998 monsoon.¹⁴ This compares with an annual incidence of 4.4 per 100 000 in the Ubon Ratchatani Province in northeastern Thailand.¹⁵

Between 1987 and 1994, 23 cases of melioidosis were diagnosed in serving members of the Singapore Armed Forces (SAF), with four deaths (17%). Unlike similar cases in the general community, most cases in the SAF occurred in otherwise fit and healthy young servicemen.¹⁶

Melioidosis has been an important cause of morbidity and mortality in foreign troops fighting in South East Asia. One report lists at least 100 cases among French troops in

Indochina between 1948 and 1954,¹⁷ and another 343 cases in American forces fighting in Vietnam by the year 1973.⁹ Melioidosis has the propensity to remain quiescent for a very long time and, like tuberculosis, may be reactivated months or years later. As there are an estimated 225 000 Vietnam veterans who are serologically positive for melioidosis, the potential for reactivated disease has been termed “the Vietnamese time bomb”.¹⁸ Disease reactivation still occurs in Vietnam veterans, but fortunately it is rare compared with the numbers exposed.¹⁹ In one case report, pulmonary melioidosis was reactivated in a subject with bronchogenic carcinoma 26 years after original exposure.²⁰ A second report involved a 76-year-old Vietnam veteran who presented with *B. pseudomallei* osteomyelitis 18 years after exposure and 10 years after a missed diagnosis of latent pulmonary disease.²¹ Another case involved septicaemic melioidosis following acute influenza A infection six years after exposure in Vietnam.²²

Melioidosis is typically distributed unevenly within endemic areas. The hyperendemicity of northeastern Thailand contrasts with central Thailand, where only a few cases of melioidosis have been reported. A closely related but non-virulent organism with similar morphology and antigenicity to the virulent *B. pseudomallei* is found in these soils, and it has recently been named *B. thailandensis*.

Closer to the Australian mainland, the incidence of melioidosis in East Timor is unknown, largely due to the effects of the recent political upheavals. Recent monitoring of refugees, peace keepers and aid workers returning from East Timor has been based at Darwin. In contrast to the numerous cases of dengue, malaria and tuberculosis, there have been no reported cases of melioidosis.⁷

Case reports from Papua New Guinea indicate that melioidosis is very uncommon in Central Province and the national referral hospital in Port Moresby, but there may be other endemic locations in the country where the extent of the disease has yet to be documented. This focal endemicity is well known in northern Australia, with less disease in the Kimberley (in the far northwest) than in the adjacent Top End.²³

Microbiological and transmission data

B. pseudomallei is an environmental saprophyte isolated from wet soils, agricultural soils, streams, pools, stagnant water and, in particular, paddy fields throughout the endemic areas. In many countries, *B. pseudomallei* is so prevalent that it is a common contaminant found in laboratory cultures.²⁴

Although in most cases there is no obvious portal of entry, such as an infected skin abrasion or wounds, the commonest route of disease transmission is nonetheless by direct inoculation of contaminated soil and water through skin abrasions or (in a military context) through combat wounds and burns, with haematogenous spread to the lungs from the local integumentary source.

Melioidosis may be transmitted by inhalation of either dust or aerosolised polluted water and this may account for cases in helicopter aircrew exposed during “dust-offs”.²⁵ In 1985 the first case report from Taiwan involved a male with rapid onset of multilobar melioidosis pneumonia after a near-drowning accident in the Philippines.²⁶ A further example of inhalational transmission involved a 24-year-old Malaysian female who developed acute non-fatal septicaemic melioidosis after inhaling infective dust during a blast injury.²⁷

An Australian study disclosed that the organism is preferentially grown from clay soils, and is most common at 25–45 cm depth.²⁸ The authors proposed that the microorganism rises to the surface during the wet season with the rising water table. However, a study in Thailand found increasing numbers of the organism at increasing depth during the wet season.²⁹

Melioidosis was first recognised within Australia in 1949 following an outbreak in sheep in northern Queensland.³⁰ Besides humans, the disease affects birds and many susceptible animals such as sheep, goats, horses, pigs and cattle. Both humans and animals acquire the disease in a similar manner—from the soil and surface water. Zoonotic transmission to humans from contact with lesion discharge of infected animals is extremely rare. While very uncommon and unusual, person-to-person transmission has occurred. An early study in the Northern Territory disclosed the presence of prostatic abscesses in 18% of men with melioidosis (far higher than is reported in other world regions), suggesting a possible role for sexual transmission of the disease.¹⁴ There have been no substantiated cases of transmission by ingestion. The organism survives for years in the soil and water, and vectors are not involved in transmission.

There are two biotypes of *B. pseudomallei*, characterised by their ability to assimilate the laevorotatory aldopentose, L-arabinose. The L-arabinose non-assimilators, Ara–, are highly virulent in some animal models and can be isolated from both clinical specimens and the environment. The Ara+ assimilators, however, are generally avirulent and found predominantly in the environment.³¹ Work in the Northern Territory found only Ara– isolates in 43 environmental samples, perhaps further evidence for the regional hyperendemicity of melioidosis.¹⁴ Isolates in Thailand generally show a greater incidence of Ara+ biotypes.

Pathophysiology

A full understanding of the pathogenesis of *B. pseudomallei* is hampered by the absence of a suitable animal model. The organism is a facultative intracellular pathogen, with a selective advantage in that it survives and flourishes inside cytoplasmic vacuoles within phagocytic cells and macrophages. However, the mechanism by which the organism may remain quiescent in a host for as long as 26 years is unknown.

The organism has been shown to form an extracellular polysaccharide capsule in response to low pH.³² Effective

phagocytosis occurs for both encapsulated and non-encapsulated forms of *B. pseudomallei*, but the addition of an exopolysaccharide may permit prolonged survival within phagosomes.³³ In addition, there is a biologically active surface lipopolysaccharide which contains two distinct O-polysaccharide antigens known as PS-I and PS-II. De Shazer et al have shown that PS-II is required for the resistance of *B. pseudomallei* to normal human serum, and so is likely to be important in disease production.³⁴

Work with animal models has thus far failed to confirm a clinically relevant exotoxin for this organism.³⁵ Flagellin proteins also exist in different strains of *B. pseudomallei*. Flagella are commonly recognised as important virulence factors expressed by bacterial pathogens, since the motility phenotype imparted by these organelles often correlates with the ability of an organism to cause disease. *B. pseudomallei* is a motile bacillus that moves by means of a polar tuft of two to four filamentous flagella. In studies of *B. pseudomallei* infection of *Acanthamoeba* trophozoites, bacterial cells attach to the amoebic surface via the distal end of their flagella. *B. pseudomallei* flagella-mediated adhesion is an essential precursor to subsequent invasion of the amoebic trophozoite, which confirms a role for flagellin in the invasion of phagocytic cells.³⁶

The importance of polymorphonuclear-initiated phagocytosis in this disease is exemplified by conditions associated with impaired phagocytic function, such as corticosteroid therapy, chronic renal disease, diabetes and excess alcohol consumption. The pivotal role played by the impairment of polymorphonuclear function in disease causation in melioidosis places it with other diseases caused by vigorous intracellular growth, such as *Listeria monocytogenes* and *Salmonella typhimurium*, where similar risk factors increase host susceptibility to disease.³⁷

Thus, the PS-II-invoked resistance to human serum, together with the capsular exopolysaccharide which encourages intracellular phagosome latency, may ultimately be shown to be partly responsible for the pathophysiology of *B. pseudomallei*.

Host risk factors and disease

There is a wide variation in susceptibility to melioidosis among both animals and humans. Native Australian marsupials, snakes, lorikeets and sulphur-crested cockatoos have all been recorded as susceptible to *B. pseudomallei*. In tropical Australia, introduced livestock are most susceptible, particularly sheep, goats and pigs, as well as camels and alpaca, while water buffalo exhibit remarkable disease resistance.³⁸

Although severe melioidosis may occur in an otherwise normal host, the fatality rate is very much higher in those with pre-existing disease risk factors. Cases without obvious risk factors were reported as 36% of the total in one Thai study³⁹ and as 20% in a Northern Territory study.⁴⁰ The most important

risk factor in humans is diabetes and this is seen in all endemic areas. In a prospective study in Darwin, Currie et al found that 37% of all patients with melioidosis had diabetes.⁴⁰

Other risk factors include excess alcohol consumption, which is particularly important in the Northern Territory, but appears less so in Thailand, Malaysia and Singapore. Chronic renal impairment and pulmonary disease also increase risk. An unusual case of fatal melioidosis associated with idiopathic pulmonary haemosiderosis was described in an indigenous Australian from Alice Springs, Northern Territory. The basis of the risk was suggested to relate to siderophore production in certain strains of *B. pseudomallei*, thereby permitting active iron scavenging from lactoferrin and transferrin and promoting growth of the organism.⁴¹

An interesting observation has implicated the recently introduced consumption of kava by Australian Aborigines in an attempt to offset the ravages of alcohol in these communities. In one study a history of kava drinking occurred in 8% of cases in the Northern Territory.⁴⁰

The melioidosis syndromes

A classification scheme for melioidosis suggested by Howe et al divided cases into acute, subacute and chronic.²⁵ More recently, the Infectious Disease Association of Thailand reported a study of 345 patients with melioidosis in which 45% had disseminated septicaemia (87% mortality), 12% had non-disseminated septicaemia (17% mortality), 42% had localised infection (9% mortality) and 0.3% had transient bacteraemia (no mortality).⁷

Subclinical infection

Melioidosis has been referred to as the great mimicker because of its protean clinical disguises. Most persons exposed to *B. pseudomallei* in the environment do not become ill.^{42,43} Using the indirect haemagglutination method, sero-epidemiological surveys around Ubon Ratchatani, northeastern Thailand, confirm widespread seropositivity among rice farmers.¹⁵ In endemic areas, seroconversion starts as soon as children are exposed to wet soil, and occurs at a rate of about 25% annually between the ages of six months and four years.⁴³ Most clinical infections are therefore not primary infections with *B. pseudomallei*.

It is unknown how many of the large asymptomatic seropositive cohort have latent infection able to reactivate, but

Clinical risk factors for infection with *B. pseudomallei*

Diabetes mellitus (most important)
Excessive alcohol consumption
Chronic renal impairment
Chronic pulmonary disease:
 chronic obstructive pulmonary disease
 idiopathic pulmonary haemosiderosis
 cystic fibrosis
Chronic heart failure
Leukaemia and lymphoma
Corticosteroid therapy
Immunodeficiency diseases
Neoplasms
Kava (*Piper methysticum*) ingestion

reactivation in the endemic areas appears to be uncommon.⁴⁴ All studies confirm that contact with the organism by those with pre-existing risk factors leads to a significantly increased risk of acute disease, which is frequently of the severe septicaemic variety.

Acute infection

Melioidosis predominantly occurs in the monsoonal wet seasons of the various endemic regions; 76% of cases in northeastern Thailand occurred in the period from June to November and 85% of cases in the Northern Territory in the months of November through to April.⁷

A study in Darwin of melioidosis over 10 years to late 1999 categorised presentations as acute (symptoms of

less than two months at presentation) or chronic (illness duration of greater than two months). In 252 cases of culture-confirmed melioidosis, 222 (88%) presented with acute disease, while 30 (12%) had chronic disease.⁴⁴ Two hundred and forty-four cases (97%) were considered to be from recent acquisition of *B. pseudomallei* infection, while only 8 (3%) were considered to be reactivation from a latent focus. Incubation ranged from 1 to 21 days, with a mean of 9 days, in the 244 reported cases of recent acquisition.

The pathology of acute infection typically exhibits necrosis, with a polymorphonuclear infiltrate and some multinucleate giant cells. Acute localised suppurative disease is often the first presentation as a painful nodule at the site of inoculation of the skin and soft tissues. Regional lymphadenitis is another form of localised disease, which likewise may suppurate, with the discharge of yellow odourless pus. The localised forms may progress to haematogenous melioidosis, thereby involving many organs, most commonly the lungs, liver and spleen.

Pneumonia is the most common clinical presentation of melioidosis in all studies throughout all endemic areas.⁴⁵ Acute pulmonary suppurative disease may follow inhalation or nasal instillation, but results much more frequently from haematogenous dissemination. Currie et al have observed that patients with septicaemic melioidosis pneumonia are often more systemically ill than the radiographic appearances of the lungs would suggest, indicating a spread to, rather than from, the lung.¹⁴

Melioidosis pneumonia is characterised by high fever, headache, severe generalised myalgia and chest pain, with either a non-productive cough or cough with copious purulent sputum often containing intermittent bright blood. X-rays may show the appearance of diffuse nodular densities (Figure 2) that may expand and coalesce and finally cavitate, forming multiple thick- and thin-walled cysts (Figure 3).



2. Radiograph of the chest, showing bilateral diffuse nodular densities, most marked in the upper left lobe.

Acute septicaemic melioidosis is the most severe disease manifestation and occurs most often against a background of diabetes, renal disease, alcoholism, leukaemia and lymphoma, corticosteroid therapy or other immunosuppressive conditions. The picture is that of septic shock, with a brief incubation period and multiorgan involvement with abscess formation. The distributive shock of sepsis is characterised by a high cardiac output, a low systemic vascular resistance and low filling pressures. It is frequently complicated by the development of irreversible organ damage and the multiple organ dysfunction syndrome (previously referred to as multiple system organ failure).⁴⁶ A primary focus may be demonstrated in about 50% of patients, most commonly in the lung, and, less frequently, in the skin or soft tissue wounds. In spite of antibiotics, vasopressors and intravenous fluid, the mortality of melioidosis septic shock is reported to vary from 84% to 100%.⁴⁰ Since the impairment of neutrophil function may be pivotal to the spread of *B. pseudomallei*, recent preliminary work has suggested that the empirical addition of granulocyte colony stimulating factor in the management of melioidosis septic shock may be of some benefit by promoting neutrophil numbers.⁴⁰

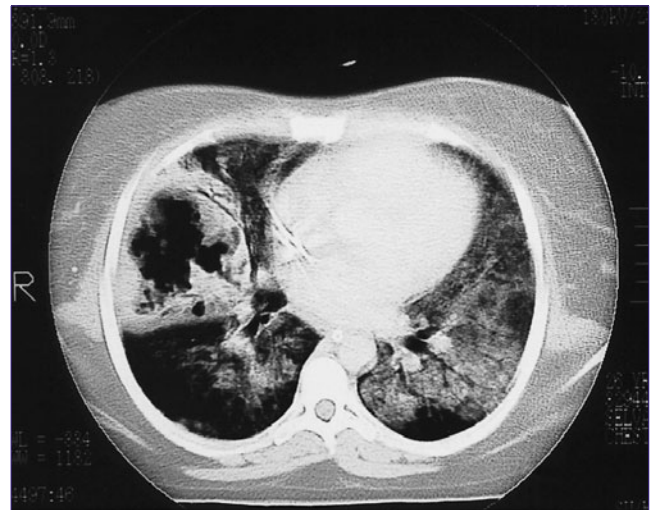
Suppurative parotitis is a form of acute primary disease seen almost exclusively in children and reported in up to 40% of cases of Thai childhood melioidosis. This syndrome is not seen in tropical Australia. Surgical drainage is required to avoid suppuration and the complication of lower motor neurone seventh-nerve palsy. A further difference in the presentations of acute primary disease between endemic areas is the frequency of acute genitourinary infection. The incidence of prostatic abscesses in Australian cases is much higher than elsewhere (Figure 4).

A less frequent acute syndrome is neurological melioidosis, accounting for 4% of melioidosis in northern Australia. Both

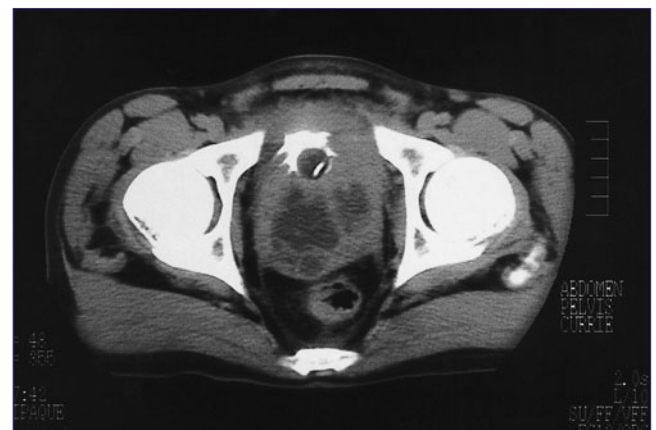
macroscopic brain abscesses and encephalitis occur. Recently, a syndrome of meningoencephalitis with varying involvement of brainstem, cerebellum and spinal cord has been identified.⁴⁷ There is no evidence of a specific strain of *B. pseudomallei* responsible for neurological melioidosis, but further studies are required to ascertain whether the apparently higher rate of neurological disease in Australia is due to a true regional difference or results from an increased clinical awareness.

Subacute infection

Subacute melioidosis is characterised pathologically by caseation necrosis and a predominantly mononuclear and plasma-cell infiltrate. This subacute suppurative form is seen most frequently within the lungs as either abscess or



3. Computed tomogram of the thorax, showing bilateral pulmonary abscess formation and cavitation due to *B. pseudomallei* infection.



4. Computed tomogram of the pelvis, showing multiple abscesses in the prostate due to *B. pseudomallei* infection.

empyema. Like the lung (Figure 5), the liver may demonstrate solitary or multiple abscess formation. Abscesses within liver or spleen have a “Swiss cheese” appearance on ultrasound. In the subacute and chronic pulmonary form, a well-recognised presentation is an upper-lobe infiltrate, with or without cavitation, closely simulating tuberculosis.

Latent or reactivated infection

Latent disease, quiescent over many years after primary exposure or the resolution of a limited primary infection, may reactivate in 3% of all cases, usually in association with an intercurrent illness, typically pulmonary disease, surgery or trauma. Late-onset diabetes, renal failure and immunosuppressant drugs may also contribute to reactivation.

Aspects of diagnosis

Melioidosis may be diagnosed by the isolation of *B. pseudomallei* from blood, sputum, pus, skin lesions or urine. The organism is a small, irregularly stained, gram-negative rod. When stained with methylene blue, *B. pseudomallei* show a characteristic bipolar or “safety-pin” configuration.

Isolation of *B. pseudomallei* is achieved by using standard culture media such as blood, MacConkey or cystine-lactose-electrolyte-deficient (CLED) agars, and routine blood culture broths. Selective media, such as modified Ashdown’s broth, are generally required for respiratory tract specimens to ensure reliable isolation from the normal or contaminating flora.⁴⁸ The organism may require 48 to 72 hours of incubation and may be easily overgrown in mixed cultures on non-selective media. The colonies are typically wrinkled, purplish and emit a musty odour (Figure 6).

Biochemical markers of *B. pseudomallei* include positive oxidase reaction, production of gas from nitrate, arginine

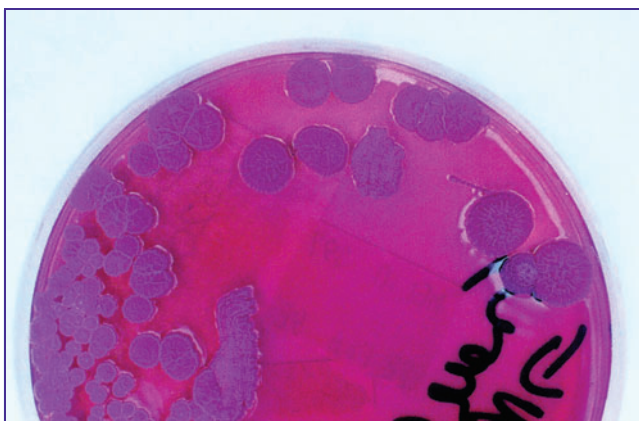


5. Lobe of lung with multiple abscess formation following *B. pseudomallei* infection.

dihydrolase and gelatinase activities and oxidation of a wide variety of carbohydrates.⁴⁹

Difficulties may arise in diagnosing culture-negative suspected melioidosis. This has led to the development of serological markers against immunodominant antigen lipopolysaccharide in the cell wall. However, serological testing in endemic areas is limited by the high latent seropositivity rates. Immunoglobulin M antibody specific to *B. pseudomallei* can be detected by enzyme immunoassay⁵⁰ and immunofluorescence.⁵¹ A latex agglutination test based on Bps-L1 monoclonal antibody that recognises capsular lipopolysaccharide antigen was reported to demonstrate 100% effectiveness in rapid identification of *B. pseudomallei* in blood cultures in endemic areas.⁵² An enzyme-linked immunosorbent assay using fluorescein isothiocyanate has been developed to detect *B. pseudomallei* antigen in urine with a sensitivity of 81% and a specificity of 96%.⁵³

Several polymerase chain reaction (PCR) techniques have been advanced, but none so far has reached clinical usage nor acceptable validation. PCR uses short specific fragments of DNA to act as primers. A *B. pseudomallei* 16S rRNA gene primer set was reported to have a sensitivity approaching 100% in 22 culture-confirmed cases of melioidosis and enabled diagnosis in three culture-negative cases. However, samples from 10 of 30 patients with other diagnoses were inexplicably positive by PCR. Thus, the advantage of rapid PCR diagnosis of melioidosis yet awaits a validated system.⁵⁴ A further report on the use of PCR using 16S rRNA gene primers, however, disclosed low sensitivities among 46 blood-culture-positive patients. The authors suggested that, in order to make PCR for melioidosis more practical, bacterial concentration steps must be added.⁵⁵



6. Growth of *B. pseudomallei* in Ashdown’s media, showing purplish wrinkled colony formation.

Management of melioidosis

Prophylaxis

There is no licensed vaccine preparation currently available for vaccination against this disease. However, possible candidates for the construction of a suitable vaccine include flagellin proteins, the endotoxin-derived O-polysaccharide antigens expressed by the organism, and flagellin-O-polysaccharide conjugates.³⁵

Antimicrobial therapy

B. pseudomallei is intrinsically resistant to many antibiotics, including the aminoglycosides, as well as the first- and second-generation cephalosporins, early beta-lactams, polymyxin and the macrolides.

Newer beta-lactams have subsequently been shown to be effective. The organism is sensitive to ceftazidime, imipenem, meropenem, piperacillin, amoxycillin-clavulanate, ceftriaxone and cefotaxime. Before 1989, “conventional therapy” for this disease consisted of a combination of predominantly bacteriostatic drugs: chloramphenicol, cotrimoxazole, doxycycline and sometimes kanamycin, given for a period of six weeks to six months.⁵⁶ The organism can develop cross-resistance to all the components of conventional drug therapy.⁵⁶

Initial intensive therapy

In 1989, White et al published the results of a randomised trial in Thailand comparing ceftazidime with so-called “conventional therapy” and showed that ceftazidime was associated with a 50% lower overall mortality in severe melioidosis.⁵⁷

A multicentre prospective randomised trial conducted by Sookpranee et al in 1992 showed that the combination of ceftazidime and trimethoprim-sulfamethoxazole was associated with similar reductions in mortality as ceftazidime alone.⁵⁸

A randomised trial comparing amoxycillin-clavulanate with ceftazidime alone in severe melioidosis showed that it was as effective during initial intensive therapy, but late treatment failures were higher, necessitating change to ceftazidime in 23% of the surviving patients.⁵⁹

In 1999, Simpson et al reported a trial of high dose imipenem versus ceftazidime and showed equal effectiveness of both drugs in severe melioidosis and fewer treatment failures with imipenem alone.⁶⁰

The present protocol at the Royal Darwin Hospital⁶¹ for the initial treatment of acute melioidosis is as follows:

Ceftazidime 2 g intravenously 6-hourly for at least 14 days (children: 50 mg/kg up to 2 g intravenously 6-hourly) *or*;

Meropenem 1 g intravenously 8-hourly for at least 14 days (children: 25 mg/kg up to 1 g) with trimethoprim-sulfamethoxazole (cotrimoxazole) 320/1600 mg orally or intravenously

12-hourly, also for at least 14 days (children: 8/40 mg/kg up to 320/1600 mg).

The duration of 14 days may be exceeded in critically ill patients, those with extensive pulmonary disease, deep-seated collections or organ abscesses, osteomyelitis, septic arthritis or neurological melioidosis.⁶²

Eradication therapy

This is required to obviate recrudescence or later relapse of melioidosis. Both the duration and the best antibiotic to use remain uncertain.⁷ Investigation of isolates from recurrent melioidosis confirms that by far the majority are true relapses from failed eradication rather than new infection.⁶³ Relapses are almost five times more common in patients with severe disease than in those with localised disease.⁶⁴

A comparative trial consisting of ciprofloxacin or ofloxacin given for maintenance therapy in adults with melioidosis for a median time of 15 weeks (range, 12–40 weeks) revealed inferior results when compared with a 20-week course of amoxycillin-clavulanic acid or the combination of chloramphenicol, doxycycline and trimethoprim-sulfamethoxazole. The authors regarded the fluoroquinolones as third-line agents.⁶⁵

A trial comparing doxycycline alone, chloramphenicol (for the first four weeks only), and a doxycycline-trimethoprim-sulfamethoxazole combination revealed a more common relapse rate among the doxycycline alone cohort. The authors suggested that doxycycline should not be used as first-line eradication therapy in melioidosis.⁶⁶

Currie et al report that the relapse rate associated with trimethoprim-sulfamethoxazole monotherapy relates almost exclusively to non-compliant patients, and they underscore the drug’s crucial role in “conventional” combination drug therapy. The current recommendation is that the eradication course should be for a minimum of three months.

Conclusion

Melioidosis is an endemic disease of tropical countries, with hyperendemic regions within Australia and Thailand. Troop deployments in South East Asia, particularly during monsoonal rains, carry an increased risk of exposure to *B. pseudomallei* via minor integumentary or major body injuries sustained during active service. Experience in the Vietnam War indicated that soldiers had widespread contact with *B. pseudomallei*, leading to active infection in smaller numbers. The incidence of melioidosis can be limited by restricting military training exercises in the tropics to non-monsoonal periods.

There is no effective vaccine for melioidosis. Australian Defence Health Service practitioners need to be aware of the vagaries of the disease if they are to prevent morbidity and mortality among service personnel.

B. pseudomallei shares some characteristics of other biological agents with potential as weapons. These characteristics include low technological requirements and costs of production, high infectivity, long environmental survival, easy dissemination by aerosol and a substantial capacity to cause illness and death. Four of the countries listed by the US government as “state sponsors of terrorism” (Iran, Iraq, North Korea and Syria) are believed to be developing botulinum toxin as a weapon, along with many other biological agents, including *B. pseudomallei*.⁶⁷

Acknowledgement

I thank Professor Bart Currie, Professor of Medicine, Menzies School of Health Research, Darwin NT, for much invaluable assistance and encouragement in the preparation of this article and for his kind permission to reproduce several photographic images.

References

- Whitmore A, Krishnaswami CS. An account of the discovery of a hitherto undescribed infective disease occurring among the population of Rangoon. *Indian Med Gazette* 1912; 47: 262-267.
- Rimington RA. Melioidosis in Northern Queensland. *Med J Aust* 1962; 1: 50-53.
- Crotty JM, Bromich AF, Quinn JV. Melioidosis in the Northern Territory; a report of two cases. *Med J Aust* 1963; 2: 274-275.
- Currie BJ. Melioidosis and the monsoon in tropical Australia. *Commun Dis Intell* 1996; 20: 63.
- Wheels M. First shots fired in biological warfare. *Nature* 1998; 395: 213.
- Srinivasan A, Kraus CN, De Shazer D, et al. *N Engl J Med* 2001; 345: 256-258.
- Currie BJ. Melioidosis. An Australian perspective of an emerging infectious disease. *Recent Advances Microbiol* 2000; 8: 5.
- Dance DA. Melioidosis as an emerging global problem. *Acta Tropica* 2000; 74: 115-119.
- Dance DA. Melioidosis. The tip of the iceberg? *Clin Microbiol Rev* 1991; 4: 52-60.
- Carlson P, Seppanen M. Melioidosis presenting as urinary tract infection in a previously healthy tourist. *Scand J Infect Dis* 2000; 32: 92-93.
- Hsueh P, Teng L, Lee L, et al. Melioidosis, an emerging infection in Taiwan? *Emerg Infect Dis* 2001; 7: 428-432.
- Leelarasamee A. Melioidosis in Southeast Asia. *Acta Tropica* 2000; 74: 129-132.
- Chaowagul W, White NJ, Dance DA, et al. Melioidosis: a major cause of community-acquired septicaemia in northeast Thailand. *J Infect Dis* 1989; 159: 890-899.
- Currie BJ, Fisher DA, Howard DM, et al. The epidemiology of melioidosis in Australia and Papua and New Guinea. *Acta Tropica* 2000; 74: 121-127.
- Suputtamongkol Y, Hall AJ, Dance DA, et al. The epidemiology of melioidosis in Ubon Ratchatani, northeast Thailand. *Int J Epidemiol* 1994; 23: 1082-1090.
- Lim MK, Tan EH, Soh CS, Chang TL. *Burkholderia pseudomallei* infection in the Singapore Armed Forces from 1987 to 1994 — an epidemiological review. *Ann Acad Med Sing* 1997; 26: 13-17.
- Rubin HL, Alexander AD, Yager RH. Melioidosis — a military problem. *Mil Med* 1963; 128: 538-542.
- Spotnitz M. Disease may be Vietnamese time bomb. *Med World News* 1966; 7: 55.
- Chodimella U, Hoppes WL, Whalen S, et al. Septicaemia and suppuration in a Vietnam veteran. *Hosp Pract* 1997; 32: 219-221.
- Mays EE, Rickets EA. Melioidosis: recrudescence associated with bronchogenic carcinoma twenty six years following initial geographic exposure. *Chest* 1975; 68: 261-263.
- Koponen MA, Zlock D, Palmer DL, Merlin TL. Melioidosis: Forgotten but not gone! *Arch Intern Med* 1991; 151: 605-608.
- Mackowiak PA, Smith JW. Septicaemic melioidosis. Occurrence following acute influenza A six years after exposure in Vietnam. *JAMA* 1978; 240: 764-766.
- Inglis TJ, Garrow SC, Henderson M, et al. *B. pseudomallei* traced to water treatment plant in Australia. *Emerg Infect Dis* 2000; 6: 56-59.
- Centers for Disease Control. Disease Information Bulletin 2001.
- Howe C, Sampath A, Spotnitz M. The *Pseudomallei* group: a review. *J Infect Dis* 1971; 124: 598-606.
- Lee N, Wu JL, Lee CH, Tsai WC. *P. pseudomallei* infection from drowning: the first reported case in Taiwan. *J Clin Microbiol* 1985; 23: 352-354.
- Wang CY, Yap BH, Delilkan AE. Melioidosis pneumonia and blast injury. *Chest* 1993; 103: 1897-1899.
- Thomas AD, Forbes Faulkner J, Parker M. Isolation of *P. pseudomallei* from clay layers at different depths. *Am J Epidemiol* 1979; 110: 515-521.
- Wuthiekanun V, Smith MD, Dance AD, White NJ. Isolation of *P. pseudomallei* from soil in north-eastern Thailand. *Trans R Soc Trop Med Hyg* 1995; 89: 41-43.
- Cottew GS. Melioidosis in sheep in Queensland. A description of the causal organism. *Aust J Exp Biol Med Sci* 1950; 28: 677-683.
- Smith MD, Angus BJ, Wuthiekanun V, White NJ. Arabinose assimilation defines a non-virulent biotype of *B. pseudomallei*. *Infect Immun* 1997; 65: 4319-4321.
- Woods DE, DeShazer D, Moore RA, et al. Current studies in the pathogenesis of melioidosis. *Microbes Infect* 1999; 1: 157-162.
- Pruksachartvuthi S, Aswapokee N, Thankerngpol K. Survival of *P. pseudomallei* in human phagocytes. *J Med Microbiol* 1990; 31: 109-114.
- De Shazer D, Brett PJ, Woods DE. The type II O-antigenic polysaccharide moiety of *B. pseudomallei* lipopolysaccharide is required for serum resistance and virulence. *Mol Microbiol* 1998; 30: 1081-1100.
- Brett PJ, Woods DE. Pathogenesis of and immunity to melioidosis. *Acta Tropica* 2000; 74: 201-210.
- Inglis TJ, Robertson TA, Woods DE. Invasion of *Acanthamoeba* cells by *B. pseudomallei* is preceded by flagella-mediated adhesion. World Melioidosis Congress, Perth, Western Australia, 2001. Abstract 77.
- Seiler P, Aignele P, Raupach BB, et al. Rapid neutrophil response controls post-replicating intracellular bacteria but not slow-replicating *Mycobacterium tuberculosis*. *J Infect Dis* 2000; 181: 671-680.
- Low Choy J, Mayo M, Janmaat A, Currie BJ. Animal melioidosis in Australia. *Acta Tropica* 2000; 74: 153-158.
- Suputtamongkol Y, Chaowagul W, Chetchotisakd P, et al. Risk factors for melioidosis and bacteraemic melioidosis. *Clin Infect Dis* 1999; 29: 408-413.
- Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical Northern Australia: a 10 year prospective study and review of the literature. *Clin Infect Dis* 2000; 31: 981-986.
- Ruchin P, Robinson J, Segasothy M, Morel F. Melioidosis in a patient with idiopathic pulmonary haemosiderosis resident in Central Australia. *Aust N Z J Med* 2000; 30: 395-396.
- Ashdown LR, Guard RW. The prevalence of human melioidosis in North Queensland. *Am J Trop Med Hyg* 1984; 33: 474-478.
- Kanaphun P, Thrawattanasuk N, et al. Serology and carriage of *P. pseudomallei*: a prospective study in 1000 hospitalised children in northeast Thailand. *J Infect Dis* 1993; 167: 230-233.
- Currie BJ, Fisher DA, Anstey NM, Jacups SP. Melioidosis: acute and chronic disease, relapse and reactivation. *Trans R Soc Trop Med Hyg* 2000; 94: 301-304.
- Dance DA. Melioidosis. *Rev Med Microbiol* 1990; 1: 143-150.
- Practice parameters for haemodynamic support of sepsis in adult patients in sepsis. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med* 1999; 27: 639-660.
- Wells R, McCormack J, Lavermore P, Tannenber A. Melioidosis causing encephalitis. *Aust N Z J Med* 1996; 26: 567-570.
- Walsh AL, Wuthiekanun V. The laboratory diagnosis of melioidosis. *Br J Biomed Sci* 1996; 53: 249-253.

49. Murray P, Baron E, Pfaller M, et al, editors. Manual of Clinical Microbiology. 6th ed. American Society for Microbiology, 1995.
50. Ashdown LR, Johnson RW, Koehler JM, Cooney CA. Enzyme-linked immunosorbent assay for the diagnosis of clinical and subclinical melioidosis. *J Infect Dis* 1989; 160: 253-260.
51. Ashdown LR. Relationship and significance of specific immunoglobulin M antibody response in clinical and subclinical melioidosis. *J Clin Microbiol* 1981; 14: 361-364.
52. Dharakul T, Songsivilai S, Smithikarn S, et al. Rapid identification of *B. pseudomallei* in blood cultures by latex agglutination using lipopolysaccharide-specific monoclonal antibody. *Am J Trop Med Hyg* 1999; 61: 658-662.
53. Aucken H, Suntharasamai P, Rajchanuwong A, White NJ. Detection of *P. pseudomallei* antigen in urine for the diagnosis of melioidosis. *Am J Trop Med Hyg* 1994; 51: 627-633.
54. Haase A, Brennan M, Barrett S, et al. Evaluation of PCR for the diagnosis of melioidosis. *J Clin Microbiol* 1998; 36: 1039-1041.
55. Kunakorn M, Raksakait K, Sethaudom C, et al. Comparison of three PCR primer sets for the diagnosis of septicemia melioidosis. *Acta Tropica* 2000; 74: 247-251.
56. Leelarasamee A, Bovornkitti S. Melioidosis: review and update. *Rev Infect Dis* 1989; 11: 413-425.
57. White N, Dance D, Chaowagagul N, et al. Halving the mortality of severe melioidosis by ceftazidime. *Lancet* 1989; 2: 697-701.
58. Sookpranee M, Boonma P, Sussaengrat W, et al. Multicenter prospective randomized trial comparing ceftazidime and cotrimoxazole with chloramphenicol, doxycycline and cotrimoxazole for the treatment of severe melioidosis. *Antimicrob Agents Chemother* 1992; 36: 158-162.
59. Suputtamongkol Y, Dance D, Chaowagul W, et al. Amoxycillin-clavulanic acid treatment of melioidosis. *Trans R Soc Trop Med Hyg* 1991; 85: 672-675.
60. Simpson A, Suputtamongkol Y, Smith M, et al. Comparison of imipenem and ceftazidime as therapy for severe melioidosis. *Clin Infect Dis* 1999; 29: 381-387.
61. Currie BJ, Fisher DA, Anstey N, et al. Melioidosis: the Top End prospective study continues into another wet season and an update on treatment guidelines. *Northern Territory Dis Control Bull* 2000; 7(4): 19-20.
62. Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical northern Australia: A 10 year prospective study and review of the literature. 2000 Writing Group, in press.
63. Desmarchelier P, Dance D, Chaowagul W, et al. Relationships among *P. pseudomallei* isolates from patients with recurrent melioidosis. *J Clin Microbiol* 1993; 31: 1592-1596.
64. Chaowagul W, Suputtamongkol Y, Dance D, et al. Relapse in melioidosis: Incidence and risk factors. *J Infect Dis* 1993; 168: 1181-1185.
65. Chaowagul W, Suputtamongkol Y, Smith M, White N. Oral fluoroquinolones for maintenance treatment of melioidosis. *Trans R Soc Trop Med Hyg* 1997; 91: 599-601.
66. Chaowagul W, Simpson A, Suputtamongkol Y, et al. A comparison of chloramphenicol, trimethoprim-sulfamethoxazole and doxycycline with doxycycline alone as maintenance therapy for melioidosis. *Clin Infect Dis* 1999; 29: 375-380.
67. United States Department of State. Patterns of global terrorism 1999. Washington, DC. The Department. <<http://www.state.gov/www/global/terrorism/1999report/1999index.html>>. Accessed 18/1/02.

(Received 8 Aug, accepted 15 Nov, 2001)



Book Review

Making a difference

Obstetrics and gynaecological surgery in the Third World. Ian Jones, Jeremy Oats and Roger Likeman. Brisbane: Mater Misericordiae Health Services, 2001.

WHEN NON-OBSTETRICALY TRAINED DOCTORS venture into the Third World for humanitarian work, one of their greatest fears is the need to confront an obstetric emergency. This new primer has been written with this nervous audience in mind. The authors have all had experience in humanitarian aid work as surgeons and two have had extensive experience in military operations when civilian services have broken down.

In a short text intended as an *aide memoire*, it is inevitable that some subjects receive less than exhaustive treatment and others are omitted. The decision to avoid any mention of operative vaginal delivery other than assisted breech delivery has been justified on grounds that inexperienced operators are more likely to cause harm. If the alternative is a difficult caesarean with the presenting part deep in the pelvis, I doubt that abdominal delivery is necessarily the "soft option".

The book is written in keeping with sound educational principles. The illustrations are easily understood and

relevant. Where a diagnosis is required, there is emphasis on the fundamentals — ie, a good history and physical examination — principles that are often given scant attention in nations with ready access to computer-aided imaging and sophisticated pathology services.

The value of freshly donated whole blood for obstetric haemorrhage is emphasised.

In accordance with the original reasons for production of this book, the ADF may distribute it to non-obstetric medical officers before deployment.

The concluding chapter has some excellent advice for the "crusader": not all your patients will survive, and debriefing is necessary for all team members when critical incidents occur. Standards of care will inevitably differ from those in the First World — but what is important is that you can still make a positive difference.

Commander Michael C O'Connor, RANR